REMARKS

CLAIM STATUS

Claims 1-7 and claims 11-13 are currently pending in the application. In order to facilitate the prosecution of this application, claims 1-7 and 11-13 have been cancelled without prejudice to the Applicants' right to pursue the subject matters in a future application. Claims 14-28 are newly added. Claim 14 is a revised version of the now cancelled claim 1. Claim 15 is a revised version of the now cancelled 3, and claim 16 is a revised version of now cancelled claim 7. Claims 17-28 correspond to subject matter claimed in the now cancelled claims 11-13. Hence, Applicants submit that no new matter has been added.

Applicants hereby respectfully request the entry of this Amendment. Upon entry of this Amendment, claims 14-28 will be pending and under examination in this application.

Rejection Under 35 U.S.C. 112, 2nd Paragraph, Indefiniteness

Claims 1-7 and 11-13 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is moot because the claims have been cancelled.

Applicants submit that the phrases in the previous claims which the Examiner references as the source of the indefiniteness, including the term "substantially the sequence", "substantially the sequence of," and "substantially comprising from amino acid 1 to 30" have been eliminated. The new claims recite amino acids which consist of the enumerated sequences as identified by

sequence ID numbers. The Examiner has stated that "The specification discloses the generation of a multimer protein comprising a plurality of proteins selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4". Accordingly, independent claim 14 recites *"a multimer protein molecule comprising a plurality of proteins having amino acid sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4".*

Rejection Under 35 U.S.C. 112, 1st Paragraph, Enablement

Claims 1-7 and 11-13 are rejected under 35 U.S.C. §112, 1st paragraph, for lack of enablement. The rejection is moot because the claims have been canceled.

The Examiner has stated that an issue remains regarding whether the multimer proteins will have medicinal and/or pharmaceutical use. The Examiner has also stated that there exists an absence of detailed description in the specification as to how to use the protein as a medicament, and that there are a lack of working examples as to treatment. The Examiner has also suggested that substantiating evidence may be in the form of animal tests and cites Ex parte Krepelka, 231 USPQ 7436 (Board of Patent Appeals and Interferences 1986).

Applicants respectfully traverse this rejection. Applicants instead submit that the in vitro histamine release assays performed with the blood of Pj-allergic subjects described in the specification (i.e. on p. 13), involving both the activity of heterotrimer clones as well as Pj 1 loop and Pj 2 loop clones, sufficiently demonstrate the advantages of the multimer

clone protein molecules over the monomeric proteins with respect to lower ability of histamine release. Also, the antibody-binding assays demonstrate success with respect to the principal objective of developing molecules with fewer side effects, i.e. less reactivity with IgE (Fig. 5). These results easily demonstrate advantages with respect to the use of such proteins when administered through specific immunotherapy - i.e. in medicinal use. In view of the data presented herein, Applicants submit that one of ordinary skill in the art would readily recognize that the proteins of the present invention will have medicinal and/or pharmaceutical use.

Applicants submit that in vivo experiments are not necessary to enable the protein for use as a medicament or pharmaceutical composition. While Ex parte Krepelka admittedly states that "Substantiating evidence may be in the form of animal tests which constitute recognized screening procedures with clear relevance to utility in humans," the rejections by the Examiner in Ex parte Krepelka on an application directed to a cancer treatment were ultimately overturned. In the application of Krepelka, the specification of the appellants' parent application set forth animal tests as well as in vitro studies, "both of which [were] asserted to be predictive with regard to utility in humans." Ex parte Krepelka at 7436.

Applicants assert that a person of ordinary skill in the art, knowledgeable with respect to the typical adjuvants and/or diluents utilized in the hypoallergenic treatment, would be able to effectively use the protein as a medicament or pharmaceutical

composition after having made appropriate patient dosing calculations.

Rejection Under 35 U.S.C. 112, 1st Paragraph, Written Description

Claims 1-7 and claims 11-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter not described in the specification to reasonably convey that the inventor, at the time the application was filed, had possession of the claimed invention. The rejection is moot because the claims have been cancelled.

The Examiner acknowledges that "Applicant is in possession of a multimer protein comprising a plurality of proteins selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3 and SEQ ID NO:4". Newly added independent claim 14 recites *"a multimer protein molecule comprising a plurality of proteins having amino acid sequences selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4"*. Hence, Applicants submit that the subject matter of the claims has been described in the specification to reasonably convey that the inventors, at the time the application was filed, had possession of the claimed invention.

Rejection Under 35 U.S.C. 103

Claims 1-7 and claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (FASEB J., Vol. 15, No. 11, Pages 2045-2047) in view of Colombo (International Archives of Allergy and Immunology, Vol. 130, No. 3, Pages 173-179). The rejection is moot because the claims have been cancelled.

Vrtala et al. teaches the formation, by genetic engineering, of a homo-dimer or trimer of the major birch pollen allergen (Bet V1), a tree pollen allergen unrelated to the Par j allergen of the present invention. The multimers consist of covalently linked copies of the allergen Bet v 1. The multimers were obtained by expressing 2 or 3 copies of Bet v 1 cDNA linked by short oligonucleotide spacers with an open reading frame, in E. coli (p. 2045, left column, second paragraph, first sentence). Vrtala et al. neither teaches that different allergens may be combined to generate an hetero-dimer or trimer, nor does Vrtala teach what properties a multimer of different allergens would have.

In addition, there does not exist sufficient motivation for persons of ordinary skill in the art to combine the teaching of Vrtala et al. to that of Columbo, because the documents relate to different technical fields. Nevertheless, if the teachings of Vrtala et al. and Columbo were combined, there would not be a reasonable chance of success with respect to a person of ordinary skill in the art deriving the present invention, which relates i) to different allergens than Bet v 1 and ii) to heterodimers, the molecules displaying hypoallergenicity. Therefore, such a combination would not have been "obvious to try."

Moreover, in the field of allergens, it is notoriously difficult to predict whether an engineered allergen may have hypoallergenic properties and the engineering of an allergen is not an obvious task. The skilled person in this field is well aware that even a small structural change in the product (a

vector, a protein, a DNA sequence) or in the procedure (purification process) can produce dramatic functional changes.

For instance, the publication Bonura et al., herein enclosed as Exhibit 1 (IAAI 2001, 9 pages), teaches that site specific mutagenesis on cysteine residues of the Parj 1 allergens is a powerful strategy to modify the stucture of an allergen, leading to reduced IgE binding activity. However, not all the introduced mutations displayed an immunological effect. In particular, when cysteines 4, 29 and 30 were disrupted, a highly reduced IgE binding activity in vitro and in vivo was observed; on the contrary, when cysteines 50 and 52 were disrupted no biological effect was obtained. Thus, disruption of disulphide bonds cannot be used as a general strategy to reduce the allergenicity of a molecule. This is in no way obvious and predictable.

In the present invention, two independent allergens with independent IgE epitopes Duro et al. FEBS Letters 199 (4 pages), herein enclosed as Exhibit 2 were combined rendering their engineering even more complex and unpredictable. Thus, the multimers of the present invention are not obvious in view of cited documents.

Conclusion

Applicants believe that all grounds of objections and rejections raised in the outstanding Office Action have been fully addressed, and the claims are in condition for allowance. Accordingly, Applicants respectfully request favorable action to be rendered by the Examiner.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below. No fee is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

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